Brain, Behavior, and Immunity 30 (2013) S109–S116

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors

Shelli Kesler [a,*], Michelle Janelsins [b], Della Koovakkattu [a], Oxana Palesh [a], Karen Mustian [b], Gary Morrow [b], Firdaus S. Dhabhar [a]

[a] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, United States
[b] Department of Radiation Oncology, University of Rochester, Rochester, NY 14642, United States

ARTICLE INFO

Article history:
Available online 12 June 2012

Keywords:
Breast cancer
Chemotherapy
Interleukin-6
Tumor necrosis factor-alpha
Memory
Hippocampus
MRI

ABSTRACT

Many survivors of breast cancer show significant cognitive impairments, including memory deficits. Inflammation induced by chemotherapy may contribute to hippocampal changes that underlie these deficits. In this cross-sectional study, we measured bilateral hippocampal volumes from high-resolution magnetic resonance images in 42 chemotherapy-treated breast cancer survivors and 35 healthy female controls. Patients with breast cancer were, on average, 4.8 ± 3.4 years off-therapy. In a subset of these participants (20 breast cancer, 23 controls), we quantified serum cytokine levels. Left hippocampal volumes and memory performance were significantly reduced and interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNFα) concentrations were significantly elevated in the breast cancer group compared to controls. In the breast cancer group, lower left hippocampal volume was associated with higher levels of TNFα and lower levels of IL-6 with a significant interaction between these two cytokines suggesting a potential modulatory effect of IL-6 on TNFα. Verbal memory performance was associated with cytokine levels and left hippocampal volume in both groups. These findings provide evidence of altered hippocampal volume and verbal memory difficulties following breast cancer chemotherapy that may be mediated by TNFα and IL-6.

1. Introduction

Cognitive impairments are a common late effect of breast cancer and its treatments affecting as many as 75% of survivors (Janelsins et al., 2011; Wefel et al., 2011). Memory impairments are among the most consistently observed difficulties following breast cancer treatment (Jansen et al., 2005; Correa and Ahles, 2008; Janelsins et al., 2011; Wefel et al., 2011) and may involve abnormality of the hippocampus, a region critical for memory function (Squire et al., 2010; Squire and Wixted, 2011). Animal models suggest that chemotherapy-related and/or pro-inflammatory cytokine neurotoxicity may specifically cause damage to the hippocampus (Tangpong et al., 2006; Winocur et al., 2006; Fardell et al., 2010; Joshi et al., 2010; Aluise et al., 2011; Seigers and Fardell, 2011).

Although chemotherapeutic agents typically have restricted direct access to brain tissue due to the blood–brain barrier (BBB), disease states such as cancer, radiation treatment, genetic variations and other factors may make the BBB more permeable to chemotherapy, or may induce alterations in endothelial cells that trigger microenvironment changes within the brain (Ahles and Saykin, 2007; Deeken and Loscher, 2007; Wefel et al., 2008). The hippocampus is unique in that it is one of the only brain regions of continued neural stem cell proliferation throughout the lifespan (Eriksson et al., 1998; Gage, 2000). Neural stem cell proliferation is very tightly regulated and highly sensitive to microenvironment changes. Although chemotherapeutic agents such as doxorubicin (one of the most common breast cancer treatments) are not known to readily cross the BBB, these drugs are associated with reduced hippocampal neurogenesis (Janelsins et al., 2010). Specifically, many chemotherapeutic agents cause neural progenitor cells to lose their capacity for self-renewal even after an initial dose, particularly in the hippocampus (Dietrich et al., 2006, 2010; Winocur et al., 2006; Seigers et al., 2008, 2009). Repetitive dosing, as most patients with breast cancer experience, causes persistent suppression of cell division in the hippocampus (Dietrich et al., 2006; Dietrich, 2010; Hyrien et al., 2010). Both dividing and non-dividing neural and glial cells are significantly vulnerable to chemotherapies (Dietrich et al., 2006, 2010; Winocur et al., 2006; Seigers

* Corresponding author. Address: 401 Quarry Road, MC5795, Stanford, CA 94305-5795, United States. Tel.: +1 650 823 1583; fax: +1 650 472 8937.
E-mail address: skesler@stanford.edu (S. Kesler).

0889-1591/$ - see front matter © 2012 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.bbi.2012.05.017

et al., 2008, 2009) and even small amounts of chemotherapy in the brain may cause long-term damage by disrupting cellular plasticity (Dietrich, 2010).

Chemotherapy also may cause indirect neurotoxic brain injury via pro-inflammatory cytokine pathways. Breast cancer chemotherapy and radiation treatments have been shown to elevate peripheral cytokine levels (Vardy et al., 2007; Seruga et al., 2008; Bower et al., 2009; Vardy, 2009; Janelsins et al., 2012). Cytokines readily cross the BBB via active transport mechanisms as well as through circumventricular regions where the BBB is less rigid (Wilson et al., 2002). Binding of cytokines to endothelial receptors in the brain vasculature with subsequent release of other mediators (e.g. chemokines, prostaglandins) leads to impairment of BBB integrity (Wong et al., 1996; Anthony et al., 1997; Konsman et al., 2004). Cytokines activate microglia and astrocytes, stimulate local inflammation and induce oxidative and nitrosative brain damage, particularly in the hippocampus (Tangpong et al., 2006, 2007; Joshi et al., 2007, 2010; Lynch, 2010; Aluise et al., 2011). Cytokine receptors are abundantly expressed in the hippocampus and increased peripheral cytokine levels have been associated with disrupted hippocampal stem cell function, reduced hippocampal volume and reduced memory performance (Das and Basu, 2008; Marsland et al., 2008; McAfoose and Baune, 2009).

Women with breast cancer are at increased risk for psychiatric distress and dysfunction of the hypothalamic–pituitary-adrenal (HPA) axis (Giese-Davis et al., 2004, 2006; Spiegel et al., 2006). HPA dysfunction in patients with breast cancer is associated with immunosuppression and impairment in cytokine regulation (Sephton et al., 2009). Abnormal diurnal cortisol patterns (indicative of HPA dysfunction) have been consistently observed among women with breast cancer (Abercrombie et al., 2004; Spiegel et al., 2006). Glucocorticoids such as cortisol tend to mediate the effects of cytokines on hippocampal memory and plasticity (Yirmiya and Goshen, 2011). Chronic stress and exposure to endogenous cortisol elevations can result in decreased hippocampal volumes (Erickson et al., 2003; Brown et al., 2004). Cortisol can also impair memory performance at low or high concentrations (Erickson et al., 2003; Lupien et al., 2005).

Although abnormal hippocampal structure and function have been noted in previous studies of breast cancer chemotherapy (McDonald et al., 2010; Bergouignan et al., 2011; de Ruiter et al., 2011), to date, there have been no investigations of the relationships between hippocampal structure and peripheral cytokine levels in breast cancer survivors. We therefore measured several serum cytokines, hippocampal volume and verbal memory performance in chemotherapy-treated breast cancer survivors and matched healthy female controls. We hypothesized that increased pro-inflammatory cytokine levels would be associated with decreased hippocampal volumes and verbal memory scores in the breast cancer group compared to the control group.

2. Methods

2.1. Participants

This study included 44 female survivors of primary (stage I-IIIA) breast cancer who all underwent surgery and adjuvant chemotherapy treatment (doxorubicin + cyclophosphamide or paclitaxel = 36; cyclophosphamide + 5-fluorouracil and paclitaxel or methotrexate = 6) who were, on average, 4.8 ± 3.4 years off-therapy (range = 1–12 years). Survivors were excluded for history of relapse or prior chemotherapy treatment and were all disease and relapse free at the time of evaluation. Also included were 38 healthy female controls. There was no significant difference between groups in terms of age (range = 41–73 years), education, global intelligence and minority status but the breast cancer group had significantly more postmenopausal women (Table 1). BC survivors were recruited via the Army of Women (http://www.armyofwomen.org/), community-based BC support groups and local media advertisements. Healthy controls were recruited via the Army of Women and local media advertisements. The Army of Women advertisement indicated that researchers at Stanford were seeking to better understand "problems related to attention, memory, depression, and anxiety" following breast cancer and its treatments. Participants were excluded for previous chemotherapy treatment, neurological, psychiatric, or medical conditions known to affect cognitive function as well as any magnetic resonance imaging (MRI) contraindications. This study was approved by the Stanford University Institutional Review Board and all participants provided informed consent.

2.2. Cognitive assessment

Memory function was measured using the Multifactorial Memory Questionnaire Ability Scale (MMQ) (Troyer and Rich, 2002) and the Hopkins Verbal Learning Test Revised (HVLT) (Wefel et al., 2011). The MMQ provides subjective assessment of one's memory abilities. The HVLT is a measure of verbal memory and learning. The HVLT Total score represents the total number of words recalled across three list learning trials and HVLT Delayed score indicates the number of words recalled following a 20 min delay. Global intelligence (IQ) was measured using a composite of the Matrix Reasoning and Information subtests of the Wechsler Adult Intelligence Scale 4th Edition (Wechsler, 2008). Participants were also administered other cognitive measures including the Wisconsin Card Sorting, Categories, Behavioral Rating Inventory of Executive Function and Verbal Fluency tests which are not reported here given that the focus of this study was on memory.

2.3. Psychiatric function

Although participants were excluded for diagnosed psychiatric disorders, the Clinical Assessment of Depression (CAD), which measures depression, anxiety and cognitive/physical fatigue (Aghakhani and Chan, 2007), was included given the known effect of these symptoms on cognitive status, hippocampal physiology and cytokine levels (Seguin et al., 2009; You et al., 2011).

2.4. MRI Acquisition

MRI scanning was performed on a research-dedicated, GE Discovery MR750 3.0 Tesla whole body scanner (GE Medical Systems, Milwaukee, WI). High-resolution T1-weighted images were acquired with 3D spoiled gradient echo pulse sequence using the following parameters: TR = 8.5 ms, TE = 3.396, TI = 400 ms, flip angle = 15°, FOV = 220 mm, number of excitation = 1, acquisition matrix = 256 × 192, 124 contiguous coronal slices, in-plane

Table 1
Participant characteristics. Data are shown as mean (standard deviation) unless otherwise indicated.

	Breast cancer	Controls	t/c^2	p
N	42	35		
Age	54.6 (6.5)	55.5 (9.3)	0.474	0.64
Education (years)	16.3 (2.6)	17.0 (2.7)	1.09	0.28
Minority status	N = 3 (7%)	N = 4 (11%)	2.63	0.62
Postmenopause	N = 33 (79%)	N = 18 (51%)	9.11	0.004
Tamoxifen	N = 22 (52%)			
Radiation	N = 29 (69%)			
Time off-therapy (years)	4.8 (3.4)			
Stage	2.12 (0.72)			

resolution = 0.859 mm × 0.859 mm. Participants also underwent T2* (BOLD) and diffusion-weighted MRI scans during this session.

2.5. Hippocampal volume measurement

Data from 3 controls and 2 breast cancer survivors were excluded from the analysis due to incidental detection of neuroanatomic abnormality. Preprocessing and hippocampal volume measurement were performed in Freesurfer v4.5 (http://surfer.nmr.mgh.harvard.edu/). Briefly, the preprocessing steps involved interpolation of images to an isotropic voxel size of 1 mm^3, non-uniform intensity correction, intensity normalization, removal of non-brain tissue and spatial normalization to standardized Talairach space. Next, segmentation of the left and right hippocampal regions for each participant was performed (Fischl et al., 2002, 2004). We then utilized Freeview, a visualization and editing tool (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeviewGuide), to manually inspect and correct the hippocampal regions of interest for errors in automated delineation (Fig. 1). Specifically, approximately 75% of the data required very minor adjustment (less than 0.2 cc difference pre and post editing) and less than 3% of the data required some adjustment (less than 0.35 cc difference pre and post editing). This step was performed by a certified rater who was blind to group membership and had demonstrated reliability with a gold standard (left hippocampus = 95.1%, right hippocampus = 97.5%) by intraclass correlation (two way mixed model, absolute agreement) (Bartko, 1966). The gold standard hippocampal delineation method was created by our group (Kates et al., 1997) and has been successfully utilized in our previous studies (Kesler et al., 2004, 2009b; Reiss et al., 2004; Aye et al., 2011). Hippocampal volume measurements included combined gray and white matter tissue.

2.6. Cytokine measurement

A subset of 23 controls and 20 breast cancer survivors underwent venipuncture for cytokine analysis. These subgroups were also matched for age, education, global intelligence and minority status but differed in terms of menopausal status. Between 9:00 and 10:00 AM, before the MRI and cognitive assessments, whole blood was collected (non-fasting) using 10 ml Vacutainer serum separator tubes (Becton Dickinson, Franklin Lakes, NJ). Following 30 min of clotting time at room temperature, serum was spun at 1300 x g for 15 min at 4 °C, aliquotted, frozen and stored at −80 °C until assayed. Interleukin (IL)-6, IL-8, IL-10, IL-12, IL-1-beta (IL-β interferon-gamma (IFNγ and tumor necrosis factor-alpha (TNFα) were quantified (pg/mL) using a high sensitivity multiplexed sandwich immunoassay (Mesoscale Discovery, Gaithersburg, MD). The blood draw was begun later in the study following the acquisition of additional funding to support these methods. Any new participants enrolled at that time were asked to provide a blood sample and none declined.

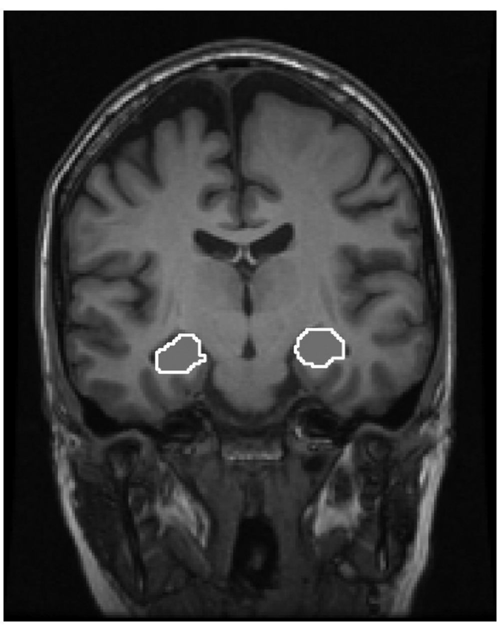

Fig. 1. Illustration of hippocampal delineation using Freesurfer (http://surfer.nmr.mgh.harvard.edu/). The image is shown in radiologic convention where the left hippocampus is shown on the right side of the image and right hippocampus is shown on the left.

2.7. Statistical analyses

For the main group (breast cancer = 42, control = 35) the following analyses were conducted. Univariate analyses of covariance in SPSS 19.0 (IBM, Armonk, NY) were used to determine group differences in IQ, total brain volume and CAD scores, controlling for age, tamoxifen (1 = yes, 0 = no), radiation (1 = yes, 0 = no) and menopausal status (1 = postmenopausal, 0 = premenopausal). Multivariate analysis of covariance (MANCOVA) was conducted to determine group differences in (1) HVLT Total and Delayed recall conditions controlling for age, tamoxifen, radiation and menopausal status, and (2) left and right hippocampal volumes controlling for total brain volume, age, tamoxifen, radiation and menopausal status. For the subgroup that had cytokine data MANCOVA was performed to examine group differences in cytokine levels controlling for age, radiation (1 = yes, 0 = no), tamoxifen, body mass index and menopausal status. We included menopausal status and tamoxifen as covariates in all analyses to conservatively account for group differences in estrogen levels (Boulware et al., 2011), particularly since groups differed in terms of menopausal status. Radiation has also been shown to impact cognitive function in breast cancer patients, including verbal memory (Quesnel et al., 2009; Phillips et al., 2012). The effects of local radiation on brain volume are unknown and therefore this relationship was also examined in exploratory analyses as described below. Cytokine levels were not normally distributed and therefore log transformed. IFNγ and IL-β levels could not be detected in 14 participants (8 controls, 6 breast cancer) and therefore these data were excluded from the analyses.

Multiple linear regression analyses (forced entry) within each subgroup (participants who had cytokine data) were used to examine effects of cytokines on hippocampal volumes and the combined effects of cytokines and hippocampal volume on memory performance. Only those cytokine, cognitive-behavioral and hippocampal variables that differed between groups as well as their interaction terms were modeled, controlled for age and total brain volume. Additionally, exploratory analyses of the effects of host (age, education, menopausal status) treatment (time off-therapy, radiation, tamoxifen), psychiatric (CAD score) and disease (stage at diagnosis) variables on cytokine levels, hippocampal volumes and memory performance were conducted using stepwise linear regressions. Backward selection was utilized and the model with the highest adjusted R^2 was selected as the best fitting. Independent variables were mean centered for all regression analyses (Kraemer and Blasey, 2004). Interaction terms were defined by multiplying the respective mean-centered variables. Finally, we conducted exploratory two-tailed Pearson correlational analyses in the main group (all participants) to examine the relationship between HVLT indices and MMQ.

3. Results

MANCOVA analyses for hippocampal volume and cytokine levels showed significant ($p < 0.05$) omnibus F statistics and therefore, results of individual variables are reported here. As shown in Table 2, left hippocampal volume was significantly reduced in the breast cancer group compared to controls ($p = 0.01$). Right hippocampal volume was marginally decreased ($p = 0.07$). Only total brain volume and age were significant covariates in the model ($p < 0.05$). Regarding cytokine levels, TNFα ($p < 0.0001$) and IL-6 ($p = 0.003$) were significantly elevated in the breast cancer group compared to controls but no other cytokine levels differed between groups (Table 3).

MANCOVA analysis for memory function assessments demonstrated significant ($p < 0.05$ omnibus F statistics and therefore, results of individual variables are reported here. The breast cancer group showed reduced HVLT Total ($p = 0.03$) and Delayed recall performances ($p = 0.02$) as well as reduced MMQ scores ($p < 0.0001$) compared to controls (Table 4).

As illustrated by Fig. 2, in the breast cancer group, lower left hippocampal volume was associated with higher levels of TNFα ($\beta = -1.56$ $p = 0.04$) and lower IL-6 ($\beta = 0.734$, $p = 0.03$). The interaction term for TNFα and IL-6 was also significant ($\beta = 1.23$, $p = 0.04$), with the total model explaining 51% of the variance (adjusted $R^2 = 0.511$, $F = 4.34$, $p = 0.02$). In controls, left hippocampal volume was not significantly associated with cytokine levels ($p > 0.20$).

Also shown in Fig. 2, lower HVLT Total performance was significantly associated with cytokine levels and left hippocampal volume (adjusted $R^2 = 0.482$, $F = 3.48$, $p = 0.04$). Only the interaction between IL-6 and TNFα ($\beta = -2.46$, $p = 0.006$) and the interaction between TNFα and left hippocampus ($\beta = 3.28$, $p = 0.05$) contributed significantly to the model. HVLT Delayed and MMQ were not associated with cytokines or hippocampal volume. In controls, increased HVLT Delayed performance was related to reduced TNFα ($\beta = -0.642$, $p = 0.009$) and increased left hippocampal volume ($\beta = 0.455$, $p = 0.05$; adjusted $R^2 = 0.268$, $F = 4.66$, $p = 0.02$). HVLT Total and MMQ performance showed no associations in the control group. HVLT indices were not significantly correlated with MMQ score in breast cancer or controls.

Exploratory analyses indicated that, in the breast cancer group, higher IL-6 was associated with older age ($\beta = 0.673$, $p = 0.004$; adjusted $R^2 = 0.414$, $F = 11.62$, $p = 0.004$). Higher TNFα was associated with older age ($\beta = 0.916$, $p = 0.001$) and shorter time off-therapy ($\beta = -0.535$, $p = 0.02$; adjusted $R^2 = 0.553$, $F = 10.29$, $p = 0.002$). There were no associations between cytokine levels and CAD score, menopause, tamoxifen, radiation or disease stage. There were no associations between CAD score, host (age, menopausal status) or disease (radiation, tamoxifen, stage, time off-therapy) variables and hippocampal volume or verbal memory function. In controls, there were no significant relationships between age, menopause, CAD score and cytokine levels, hippocampal volumes or memory function in controls.

Table 2
Total brain and hippocampal volumes (cubic centimeters).

	Breast cancer	Controls	F	p
N	42	35		
Total brain	1176 (97)	1184 (101)	0.159	0.69
Left hippocampus	4.37 (0.40)	4.68 (0.49)	6.88	0.01
Right hippocampus	4.36 (0.41)	4.61 (0.53)	3.35	0.07

Data are shown as marginal means after removing the effects of covariates and (standard deviation).

Table 3
Serum cytokine levels (pg/mL).

N	BC 20		CON 23		F	p
	Log trans.	Raw	Log trans.	Raw		
IL-6	0.21 (0.32)	1.1 (1.1)	−0.28 (0.21)	1.4 (2.8)	10.33	0.003
IL-8	0.83 (0.21)	9.0 (4.5)	0.99 (0.21)	10.2 (6.7)	1.46	0.24
IL-10	0.42 (0.55)	7.9 (16.7)	0.31 (0.35)	14.9 (2.9)	0.146	0.71
IL-12	0.30 (0.66)	10.8 (32.5)	0.31 (0.48)	3.8 (5.6)	0.001	0.98
TNFα	0.93 (0.23)	6.7 (7.5)	0.56 (0.08)	5.1 (1.1)	16.70	<0.0001

Cytokine levels were log transformed for analyses and are shown here as mean after removing the effects of covariates and (standard deviation). Statistics are shown for log transformed data only.

Table 4
Cognitive-behavioral data.

	Breast cancer	Controls	F	p
N	42	35		
HVLT-R Total recall	49.3 (8.0)	57.1 (9.6)	4.85	0.03
HVLT-R Delayed recall	49.8 (6.4)	56.0 (8.1)	6.31	0.02
MMQ	42.2 (11.2)	59.3 (7.4)	30.3	<0.0001
IQ	112 (11)	115 (13)	1.12	0.29
CAD	50.6 (12.0)	45.9 (8.1)	1.62	0.21

Data are shown as marginal means after removing the effects of covariates and (standard deviation). HVLT-R = Hopkins Verbal Learning Test Revised, MMQ = Multifactorial Memory Questionnaire Ability Scale, IQ = Matrix Reasoning and Information subtests of the Wechsler Adult Intelligence Scale 4th Edition, CAD = Clinical Assessment of Depression.

4. Discussion

The present study demonstrated significantly reduced left hippocampal volume and reduced memory performance as well as significantly elevated IL-6 and TNFα in chemotherapy-treated breast cancer survivors compared to healthy female controls. Cytokine levels were associated with left hippocampal volume in the breast cancer group. Verbal memory performance was associated with cytokine levels and hippocampal volume in both groups. These findings provide novel information regarding the mechanisms underlying memory impairment following breast cancer chemotherapy.

Our findings of reduced hippocampal volume are consistent with previous studies that utilized alternate but complementary neuroimaging analysis methods (McDonald et al., 2010; Bergouignan et al., 2011). The McDonald et al. (2010) study indicated that reduction of gray matter volume in mesial temporal regions (including hippocampus) occurred by 1 month post-chemotherapy and did not show recovery unlike other brain regions (McDonald et al., 2010). Likewise, the present findings show evidence of reduced hippocampal volume in survivors who were, on average, 5 years off-therapy. Due to the limitations of these neuroimaging methods, it is unknown whether the hippocampal volume reduction was related to reduced stem cell proliferation. Microscopic and/or fMRI studies are required to examine the dentate gyrus (hippocampal region of neurogenesis) more specifically. Hippocampal volume was not associated with time off-therapy and therefore does not likely continue to decline (or recover) over time. Importantly, our findings uniquely contribute to and extend the cancer and cognition literature by showing relationships between

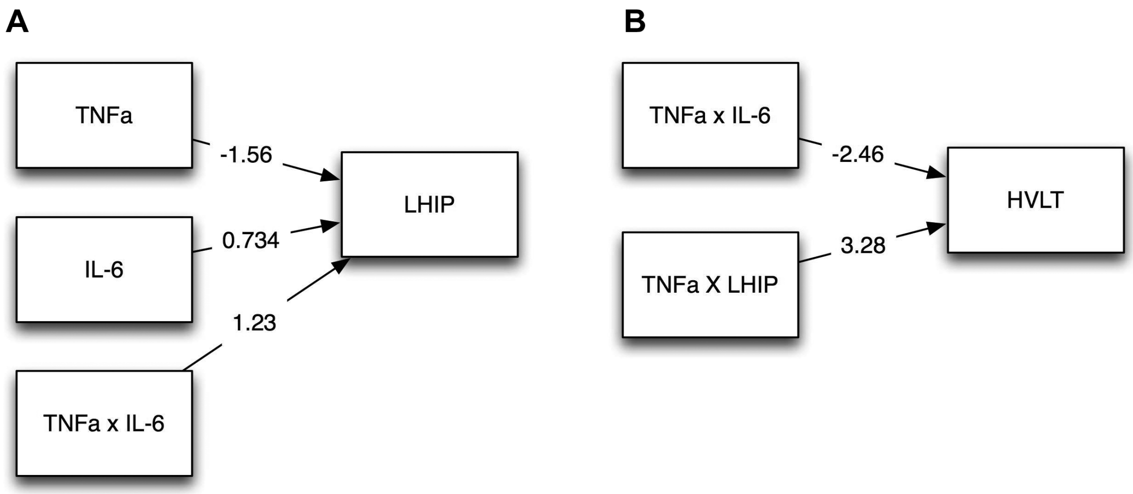

Fig. 2. In breast cancer survivors, (A) lower peripheral interleukin-6 (IL-6) and higher tumor necrosis factor-alpha (TNFα) levels were associated with lower left hippocampal (LHIP) volume. (B) Interactions between cytokines and left hippocampal volume were associated with reduced performance on the Hopkins Verbal Learning Test (HVLT).

inflammatory cytokine levels, hippocampal volume and verbal memory function.

The majority of participants in our breast cancer sample received doxorubicin based chemotherapy, which is not known to cross the blood–brain barrier but has been associated with increased cytokine expression compared to other chemotherapy regimens (Janelsins et al., 2012). Doxorubicin has been shown to elevate TNFα in animal models, particularly in the hippocampus, through oxidative modification of key plasma proteins that inhibit pro-inflammatory cytokine expression (Tangpong et al., 2006; Joshi et al., 2010; Aluise et al., 2011). Elevated TNFα has been associated with hippocampal damage in animals and may play a particularly detrimental role in neurotoxicity during early stages of brain injury (Pickering and Oconnor, 2007). Accordingly, we observed significantly elevated TNFα levels compared to healthy controls as well as an association between lower left hippocampal volumes and higher TNFα in the breast cancer group. Additionally, we found a relationship between shorter time off-therapy and increased TNFα, consistent with a potentially earlier detrimental effect of TNFα (Pickering and Oconnor, 2007).

Some patients received cyclophosphamide, fluorouracil and/or methotrexate therapies which are known to cross the blood-barrier and reduce hippocampal neurogenesis (Seigers et al., 2009; Dietrich, 2010; Janelsins et al., 2010; Seigers and Fardell, 2011). Methotrexate has some anti-inflammatory properties and has been shown to modulate IL-6 and TNFα secretion (Phillips et al., 2003). Methotrexate therapies may show less cytokine inducement compared to doxorubicin, cyclophosphamide and fluorouracil (Janelsins et al., 2012). Thus, chemotherapeutic agents may have differential effects on hippocampal physiology depending on their specific combination of neurotoxic and cytokine modulation properties. Removing the six participants who had methotrexate chemotherapy from the cytokine analysis did not change our results. Further study regarding the effects of specific chemotherapeutic agents on cytokine expression and hippocampal volume is required.

However, lower left hippocampal volume was associated with *lower* IL-6 despite IL-6 also being elevated in breast cancer survivors compared to controls. These findings are in contrast to a previous study of healthy adults showing an inverse relationship between IL-6 and hippocampal volume (Marsland et al., 2008). However, IL-6 has both pro-inflammatory and anti-inflammatory functions following brain injury and may demonstrate altered patterns of influence in individuals with histories of significant disease (Bauer et al., 2007; McAfoose and Baune, 2009). Previous studies have indicated diminished neuroprotection in the hippocampus among IL-6 deficient mice as well as a modulatory effect of IL-6 on TNFα-induced hippocampal injury (Jean Harry et al., 2003; Funk et al., 2011). Interestingly, we found a significant interaction for TNFα and IL-6 in the breast cancer group suggesting that IL-6 may modulate the effects of TNFα on the hippocampus following breast cancer and chemotherapy.

The impact of treatment-induced cytokine expression has been theorized for the past decade (Ahles and Saykin, 2007; Vardy et al., 2007; Seruga et al., 2008; Wefel et al., 2008; Vardy, 2009; Janelsins et al., 2011). Previous studies have also reported elevated pro-inflammatory cytokines in breast cancer survivors at long-term follow-up. For example, Bower and colleagues demonstrated significantly elevated markers of pro-inflammatory cytokine activity in survivors who were also an average of 5 years off-therapy (Bower et al., 2002). However, this study represents the first to identify an association between elevated cytokines and brain changes following breast cancer chemotherapy in humans. Our findings suggest that the mechanism underlying verbal memory dysfunction in breast cancer survivors may involve treatment-induced pro-inflammatory cytokine elevation that directly or indirectly damages the hippocampus which then has reduced ability to support verbal memory function. This is consistent with animal studies suggesting that cancer treatments increase cytokine levels and these cytokines cross the blood–brain barrier and induce damage to the hippocampus (Tangpong et al., 2007; Joshi et al., 2010; Lynch, 2010). Shorter time off-therapy, but not disease stage, was associated with increased TNFα in the present study indicating that during later stages, treatment rather than the disease itself is a critical inducer of pro-inflammatory cytokines and their deleterious effects. Accordingly, previous studies have shown specific effects of chemotherapy on brain structure and function as well as memory performance in breast cancer survivors after accounting for the effects of disease (Ahles et al., 2010; McDonald et al., 2010; Deprez et al., 2011, 2012; Hedayati et al., 2011; Kesler et al., 2011).

Hippocampal volume has been shown to be more strongly related to delayed verbal memory (Wolk and Dickerson, 2011). Immediate verbal memory tends to rely more on distributed brain regions including prefrontal and parietal cortices in addition to hippocampus (Wolk and Dickerson, 2011). The control group showed the expected relationship between hippocampal volume and delayed rather than immediate verbal memory but the breast cancer group showed the reverse. It is unclear why this was the case but could suggest that elevated cytokine levels disrupt typical hippocampal mechanisms in patients with breast cancer. Our previous research indicates altered neurobiology underlying different stages of verbal memory among breast cancer survivors (Kesler et al., 2009a). Further studies are required to help dissociate the different neural mechanisms involved in various stages of verbal memory encoding and recall.

A previous study showed that radiotherapy alone was associated with reduced verbal memory in breast cancer patients (Quesnel et al., 2009). A majority of participants in the present study received radiation treatment but analyses revealed no relationships between radiation, hippocampal volume or cytokine levels. There were likely too few participants in the present sample who did not have radiation to appropriately power these analyses, particularly with respect to cytokine levels. A previous study showed no effects of local radiation on cytokine levels in patients with breast cancer (Geinitz et al., 2001) although other studies have demonstrated increased inflammatory markers during radiotherapy in patients with breast or prostate cancers (Bower et al., 2009; Lopes and Callera, 2011). Further studies are required to determine the contribution of radiation therapy to cytokine levels and neurobiologic outcome following breast cancer.

Approximately 79% of our breast cancer sample was postmenopausal and postmenopausal women often show increased cognitive deficits and hippocampal atrophy attributed to estrogen deficiency (Eberling et al., 2003; Goto et al., 2011). Postmenopausal women with breast cancer taking tamoxifen (a selective estrogen receptor modulator) were shown to have reduced hippocampal volumes and greater cognitive impairment compared to control groups in previous studies (Eberling et al., 2004; Schilder et al., 2010). Additionally, estrogen is believed to play a role in cytokine modulation (Czlonkowska et al., 2005). Approximately 52% of our BC sample had a history of tamoxifen treatment and six of these participants were still taking tamoxifen at the time of evaluation. Our analyses indicated that menopausal status and tamoxifen treatment were not associated with cytokine levels, hippocampal volume or memory performance. Other studies have also demonstrated a lack of association between tamoxifen and cognitive outcome (Ahles et al., 2002; Tchen et al., 2003; Hermelink et al., 2008; Jenkins et al., 2008; Phillips et al., 2012). However, measurement of actual estrogen levels may be important for future studies of hippocampal physiology, inflammation and memory function in breast cancer.

An age-related increase in cytokine levels was noted in the breast cancer group but not in controls. Hippocampal physiology is altered in individuals with age-related neurodegenerative conditions (Hanseeuw et al., 2011; Sabuncu et al., 2011) and may mediate normal age-related cognitive decline (Ta et al., in press; Tsukiura et al., 2011; Wimmer et al., in press; Giovanello and Schacter, 2012). Previous studies have indicated a shift to a more pro-inflammatory state associated with normal aging that may alter hippocampal function (Lynch, 2010; Viviani and Boraso, 2011). For breast cancer survivors, treatments may interact with age to increase cytokine levels or may accelerate the age-related imbalance in pro-inflammatory cytokine expression.

Our present findings suggest immune dysregulation and increased pro-inflammation may contribute to the increased vulnerability of older breast cancer patients for cognitive impairment that has been observed in previous studies (Ahles et al., 2010; Kesler et al., 2011). This fits with the age-based hypothesis of neurodegeneration proposed by Herrup (Herrup, 2010). Within this model, cancer and/or its treatments could represent a precipitating injury or deviation from the normal aging process. In an age-weakened brain, this injury results in a chronic shift to a pro-inflammatory state that in turn results in accelerated neuronal loss and cognitive decline (Herrup, 2010). Herrup's model was designed to explain Alzheimer's dementia but there is some evidence (although controversial) that chemotherapy-treated breast cancer survivors are at increased risk for developing dementia compared to non-chemotherapy treated survivors (Heck et al., 2008; Du et al., 2010). Additionally, the presence of the apolipoprotein E4 allele is a common risk factor for dementia as well as chemotherapy-related cognitive dysfunction (Ahles et al., 2003). The interaction between age, cancer, chemotherapy, immune dysregulation and cognitive decline is an essential area of continued research.

An accelerated shift to a chronic inflammatory state may help explain why cytokine levels would remain elevated so long after treatment has ended. Another possibility is that cancer and/or its treatment specifically alter immune system function such that cytokine levels do not return to normal. Initial cytokine elevation may increase symptom/side effect burden (e.g. cognitive dysfunction, depression, fatigue, pain) resulting in further cytokine release with symptoms and cytokines perpetuating each other. Continued research in this area is required to determine the mechanisms of chronic cytokine elevation following breast cancer and chemotherapy.

There are several limitations of this study. The cross-sectional design limits interpretations regarding treatment effects on hippocampal volume, cytokine levels and memory function. The small sample size (especially of cytokine levels) may have reduced statistical power for detecting certain smaller effects and thus these results should be considered preliminary. Our study advertisements included statements regarding a focus that included memory problems and therefore the sample may have been biased towards survivors who were concerned about their memory function. As with many studies of breast cancer survivors, our sample was very heterogeneous in terms of disease, host and treatment variables. Information regarding specific treatment regimens (e.g. number of cycles, doses) and endocrine function (e.g. estrogen levels, years post-menopause) that may be important mediators of main effects were not available. Peripheral cytokine levels have been shown to relate to hippocampal physiology in previous studies as noted above but do not provide assessment of actual brain levels of inflammatory markers. It is unknown why IFNγ and IL-β levels could not be detected in this sample. Also, screening instruments such as the CAD may not be sufficient for detecting psychiatric disorders following breast cancer (Palmer et al., 2011). Longitudinal studies that combine neuroimaging with cytokine quantification are required in larger samples to further investigate the effects of chemotherapy and inflammation on neurobiology and cognitive outcome.

Despite these limitations, this study provides further evidence of brain injury following breast cancer and chemotherapy as well as novel, preliminary support for the role of pro-inflammatory cytokines in this brain injury and subsequent verbal memory deficit. Increased cytokine levels and reduced left hippocampus volume were observed in chemotherapy-treated breast cancer survivors even after controlling for other breast cancer treatments including radiation and tamoxifen. Cytokine levels and hippocampal volumes were associated with verbal memory functioning and therefore, these results contribute important information regarding the mechanisms underlying cognitive deficit following breast cancer chemotherapy. Continued research could potentially identify patients at high risk for cytokine dysfunction and guide treatment protocols for helping to improve or prevent cognitive difficulties in cancer survivors.

Conflicts of interest

All authors declare that there are no conflicts of interest.

Acknowledgements

This research was supported by the National Institutes of Health Director's New Innovator Award (1 DP2 OD004445-01 to SK) and the Stanford Cancer Institute's Developmental Cancer Research Award (to SK).

References

Abercrombie, H.C., Giese-Davis, J., Sephton, S., Epel, E.S., Turner-Cobb, J.M., Spiegel, D., 2004. Flattened cortisol rhythms in metastatic breast cancer patients. Psychoneuroendocrinology 29, 1082–1092.

Aghakhani, A., Chan, E.K., 2007. Test Reviews: Bracken, B.A., Howell, K. (2004). Clinical Assessment of Depression. Odessa, FL: Psychological Assessment Resources. J. Psycho. Assess. 25, 416–422.

Ahles, T.A., Saykin, A.J., 2007. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat. Rev. Cancer 7, 192–201.

Ahles, T.A., Saykin, A.J., Furstenberg, C.T., Cole, B., Mott, L.A., Skalla, K., Whedon, M.B., Bivens, S., Mitchell, T., Greenberg, E.R., Silberfarb, P.M., 2002. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. J. Clin. Oncol. 20, 485–493.

Ahles, T.A., Saykin, A.J., McDonald, B.C., Li, Y., Furstenberg, C.T., Hanscom, B.S., Mulrooney, T.J., Schwartz, G.N., Kaufman, P.A., 2010. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J. Clin. Oncol. 28, 4434–4440.

Ahles, T.A., Saykin, A.J., Noll, W.W., Furstenberg, C.T., Guerin, S., Cole, B., Mott, L.A., 2003. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. Psycho-oncology 12, 612–619.

Aluise, C.D., Miriyala, S., Noel, T., Sultana, R., Jungsuwadee, P., Taylor, T.J., Cai, J., Pierce, W.M., Vore, M., Moscow, J.A., St Clair, D.K., Butterfield, D.A., 2011. 2-Mercaptoethane sulfonate prevents doxorubicin-induced plasma protein oxidation and TNF-alpha release: implications for the reactive oxygen species-mediated mechanisms of chemobrain. Free Radical Biol. Med. 50, 1630–1638.

Anthony, D.C., Bolton, S.J., Fearn, S., Perry, V.H., 1997. Age-related effects of interleukin-1 beta on polymorphonuclear neutrophil-dependent increases in blood-brain barrier permeability in rats. Brain 120 (Pt 3), 435–444.

Aye, T., Park, Y., Kesler, S., Reiss, A.L., Schleifer, K., Baumgartner, H., Hoang, S., Wilson, D.M., Drobny, J., Buckingham, B.A., 2011. The feasibility of detecting neuropsychologic and neuroanatomic effects of type 1 diabetes in young children. Diabetes Care 34, 1458–1462.

Bartko, J.J., 1966. The intraclass correlation coefficient as a measure of reliability. Psychol. Rep. 19, 3–11.

Bauer, S., Kerr, B.J., Patterson, P.H., 2007. The neuropoietic cytokine family in development, plasticity, disease and injury. Nat. Rev. Neurosci. 8, 221–232.

Bergouignan, L., Lefranc, J.P., Chupin, M., Morel, N., Spano, J.P., Fossati, P., 2011. Breast cancer affects both the hippocampus volume and the episodic autobiographical memory retrieval. PLoS One 6, e25349.

Boulware, M.I., Kent, B.A., Frick, K.M., 2011. The impact of age-related ovarian hormone loss on cognitive and neural function. Curr. Top. Behav. Neurosci.

Bower, J.E., Ganz, P.A., Aziz, N., Fahey, J.L., 2002. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom. Med. 64, 604–611.

Bower, J.E., Ganz, P.A., Tao, M.L., Hu, W., Belin, T.R., Sepah, S., Cole, S., Aziz, N., 2009. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clin. Cancer Res.: J. Am. Assoc.Cancer Res. 15, 5534–5540.

Brown, E.S., D, J.W., Frol, A., Bobadilla, L., Khan, D.A., Hanczyc, M., Rush, A.J., Fleckenstein, J., Babcock, E., Cullum, C.M., 2004. Hippocampal volume, spectroscopy, cognition, and mood in patients receiving corticosteroid therapy. Biol. Psychiatry 55, 538–545.

Correa, D.D., Ahles, T.A., 2008. Neurocognitive changes in cancer survivors. Cancer J. 14, 396–400.

Czlonkowska, A., Ciesielska, A., Gromadzka, G., Kurkowska-Jastrzebska, I., 2005. Estrogen and cytokines production – the possible cause of gender differences in neurological diseases. Curr. Pharm. Des. 11, 1017–1030.

Das, S., Basu, A., 2008. Inflammation: a new candidate in modulating adult neurogenesis. J. Neurosci. Res. 86, 1199–1208.

de Ruiter, M.B., Reneman, L., Boogerd, W., Veltman, D.J., van Dam, F.S., Nederveen, A.J., Boven, E., Schagen, S.B., 2011. Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. Hum. Brain Mapp. 32, 1206–1219.

Deeken, J.F., Loscher, W., 2007. The blood-brain barrier and cancer: transporters, treatment, and Trojan horses. Clin. Cancer Res. 13, 1663–1674.

Deprez, S., Amant, F., Smeets, A., Peeters, R., Leemans, A., Van Hecke, W., Verhoeven, J.S., Christiaens, M.R., Vandenberghe, J., Vandenbulcke, M., Sunaert, S., 2012. longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. J. Clin. Oncol. 30, 274–281.

Deprez, S., Amant, F., Yigit, R., Porke, K., Verhoeven, J., Van den Stock, J., Smeets, A., Christiaens, M.R., Leemans, A., Van Hecke, W., Vandenberghe, J., Vandenbulcke, M., Sunaert, S., 2011. Chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients. Hum. Brain Mapp. 32, 480–493.

Dietrich, J., 2010. Chemotherapy associated central nervous system damage. Adv. Exp. Med. Biol. 678, 77–85.

Dietrich, J., Han, R., Yang, Y., Mayer-Proschel, M., Noble, M., 2006. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. J. Biol. 5, 22.

Du, X.L., Xia, R., Hardy, D., 2010. Relationship between chemotherapy use and cognitive impairments in older women with breast cancer: findings from a large population-based cohort. Am. J. Clin. Oncol. 33, 533–543.

Eberling, J.L., Wu, C., Haan, M.N., Mungas, D., Buonocore, M., Jagust, W.J., 2003. Preliminary evidence that estrogen protects against age-related hippocampal atrophy. Neurobiol. Aging 24, 725–732.

Eberling, J.L., Wu, C., Tong-Turnbeaugh, R., Jagust, W.J., 2004. Estrogen- and tamoxifen-associated effects on brain structure and function. Neuroimage 21, 364–371.

Erickson, K., Drevets, W., Schulkin, J., 2003. Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. Neurosci. Biobehav. Rev. 27, 233–246.

Eriksson, P.S., Perfilieva, E., Bjork-Eriksson, T., Alborn, A.M., Nordborg, C., Peterson, D.A., Gage, F.H., 1998. Neurogenesis in the adult human hippocampus. Nat. Med. 4, 1313–1317.

Fardell, J.E., Vardy, J., Logge, W., Johnston, I., 2010. Single high dose treatment with methotrexate causes long-lasting cognitive dysfunction in laboratory rodents. Pharmacol. Biochem. Behav. 97, 333–339.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A.M., 2004. Automatically parcellating the human cerebral cortex. Cereb. Cortex 14, 11–22.

Funk, J.A., Gohlke, J., Kraft, A.D., McPherson, C.A., Collins, J.B., Jean Harry, G., 2011. Voluntary exercise protects hippocampal neurons from trimethyltin injury: possible role of interleukin-6 to modulate tumor necrosis factor receptor-mediated neurotoxicity. Brain Behav. Immun. 25, 1063–1077.

Gage, F.H., 2000. Mammalian neural stem cells. Science 287, 1433–1438.

Geinitz, H., Zimmermann, F.B., Stoll, P., Thamm, R., Kaffenberger, W., Ansorg, K., Keller, M., Busch, R., van Beuningen, D., Molls, M., 2001. Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. Int. J. Radiat. Oncol. Biol. Phys. 51, 691–698.

Giese-Davis, J., Sephton, S.E., Abercrombie, H.C., Duran, R.E., Spiegel, D., 2004. Repression and high anxiety are associated with aberrant diurnal cortisol rhythms in women with metastatic breast cancer. Health Psychol. 23, 645–650.

Giese-Davis, J., Wilhelm, F.H., Conrad, A., Abercrombie, H.C., Sephton, S., Yutsis, M., Neri, E., Taylor, C.B., Kraemer, H.C., Spiegel, D., 2006. Depression and stress reactivity in metastatic breast cancer. Psychosom. Med. 68, 675–683.

Giovanello, K.S., Schacter, D.L., 2012. Reduced specificity of hippocampal and posterior ventrolateral prefrontal activity during relational retrieval in normal aging. J. Cogn. Neurosci. 24, 159–170.

Goto, M., Abe, O., Miyati, T., Inano, S., Hayashi, N., Aoki, S., Mori, H., Kabasawa, H., Ino, K., Yano, K., Iida, K., Mima, K., Ohtomo, K., 2011. 3 Tesla MRI detects accelerated hippocampal volume reduction in postmenopausal women. J. Magn. Reson. Imaging – JMRI 33, 48–53.

Hanseeuw, B.J., Van Leemput, K., Kavec, M., Grandin, C., Seron, X., Ivanoiu, A., 2011. Mild Cognitive Impairment: Differential Atrophy in the Hippocampal Subfields. AJNR – Am. J. Neuroradiol. 32, 1658–1661.

Heck, J.E., Albert, S.M., Franco, R., Gorin, S.S., 2008. Patterns of dementia diagnosis in surveillance, epidemiology, and end results breast cancer survivors who use chemotherapy. J. Am. Geriatr. Soc. 56, 1687–1692.

Hedayati, E., Alinaghizadeh, H., Schedin, A., Nyman, H., Albertsson, M., 2011. Effects of adjuvant treatment on cognitive function in women with early breast cancer. Eur. J. Oncol. Nurs. 16, 315–322.

Hermelink, K., Henschel, V., Untch, M., Bauerfeind, I., Lux, M.P., Munzel, K., 2008. Short-term effects of treatment-induced hormonal changes on cognitive function in breast cancer patients: results of a multicenter, prospective, longitudinal study. Cancer 113, 2431–2439.

Herrup, K., 2010. Reimagining Alzheimer's disease–an age-based hypothesis. J. Neurosci. 30, 16755–16762.

Hyrien, O., Dietrich, J., Noble, M., 2010. Mathematical and experimental approaches to identify and predict the effects of chemotherapy on neuroglial precursors. Cancer Res. 70, 10051–10059.

Janelsins, M.C., Kohli, S., Mohile, S.G., Usuki, K., Ahles, T.A., Morrow, G.R., 2011. An update on cancer- and chemotherapy-related cognitive dysfunction: current status. Semin. Oncol. 38, 431–438.

Janelsins, M.C., Mustian, K.M., Palesh, O.G., Mohile, S.G., Peppone, L.J., Sprod, L.K., Heckler, C.E., Roscoe, J.A., Katz, A.W., Williams, J.P., Morrow, G.R., 2012. Differential expression of cytokines in breast cancer patients receiving different chemotherapies: implications for cognitive impairment research. Support. Care Cancer 20, 831–839.

Janelsins, M.C., Roscoe, J.A., Berg, M.J., Thompson, B.D., Gallagher, M.J., Morrow, G.R., Heckler, C.E., Jean-Pierre, P., Opanashuk, L.A., Gross, R.A., 2010. IGF-1 partially restores chemotherapy-induced reductions in neural cell proliferation in adult C57BL/6 mice. Cancer Invest. 28, 544–553.

Jansen, C.E., Miaskowski, C., Dodd, M., Dowling, G., Kramer, J., 2005. A metaanalysis of studies of the effects of cancer chemotherapy on various domains of cognitive function. Cancer 104, 2222–2233.

Jean Harry, G., Bruccoleri, A., Lefebvre d'Hellencourt, C., 2003. Differential modulation of hippocampal chemical-induced injury response by ebselen, pentoxifylline, and TNFalpha-, IL-1alpha-, and IL-6-neutralizing antibodies. J. Neurosci. Res. 73, 526–536.
Jenkins, V.A., Ambroisine, L.M., Atkins, L., Cuzick, J., Howell, A., Fallowfield, L.J., 2008. Effects of anastrozole on cognitive performance in postmenopausal women: a randomised, double-blind chemoprevention trial (IBIS II). Lancet Oncol. 9, 953–961.
Joshi, G., Aluise, C.D., Cole, M.P., Sultana, R., Pierce, W.M., Vore, M., St Clair, D.K., Butterfield, D.A., 2010. Alterations in brain antioxidant enzymes and redox proteomic identification of oxidized brain proteins induced by the anti-cancer drug adriamycin: implications for oxidative stress-mediated chemobrain. Neuroscience 166, 796–807.
Joshi, G., Hardas, S., Sultana, R., St Clair, D.K., Vore, M., Butterfield, D.A., 2007. Glutathione elevation by gamma-glutamyl cysteine ethyl ester as a potential therapeutic strategy for preventing oxidative stress in brain mediated by in vivo administration of adriamycin: Implication for chemobrain. J. Neurosci. Res. 85, 497–503.
Kates, W.R., Abrams, M.T., Kaufmann, W.E., Breiter, S.N., Reiss, A.L., 1997. Reliability and validity of MRI measurement of the amygdala and hippocampus in children with fragile X syndrome. Psychiatry Res. 75, 31–48.
Kesler, S.R., Bennett, F.C., Mahaffey, M.L., Spiegel, D., 2009a. Regional brain activation during verbal declarative memory in metastatic breast cancer. Clin. Cancer Res. 15, 6665–6673.
Kesler, S.R., Garrett, A., Bender, B.G., Yankowitz, J., Zeng, S.M., Reiss, A.L., 2004. Amygdala and hippocampal volumes in Turner syndrome: a high-resolution MRI study of X-monosomy. Neuropsychologia 42, 1971–1978.
Kesler, S.R., Kent, J.S., O'Hara, R., 2011. Prefrontal cortex and executive function impairments in primary breast cancer. Arch. Neurol. 68, 1447–1453.
Kesler, S.R., Schwartz, C., Stevenson, R.E., Reiss, A.L., 2009b. The impact of spermine synthase (SMS) mutations on brain morphology. Neurogenetics 10, 299–305.
Konsman, J.P., Vigues, S., Mackerlova, L., Bristow, A., Blomqvist, A., 2004. Rat brain vascular distribution of interleukin-1 type-1 receptor immunoreactivity: relationship to patterns of inducible cyclooxygenase expression by peripheral inflammatory stimuli. J. Comp. Neurol. 472, 113–129.
Kraemer, H.C., Blasey, C.M., 2004. Centring in regression analyses: a strategy to prevent errors in statistical inference. Int. J. Methods Psychiatr. Res. 13, 141–151.
Lopes, C.O., Callera, F., 2011. Three-dimensional conformal radiotherapy in prostate cancer patients: rise in interleukin 6 (IL-6) but not IL-2, IL-4, IL-5, tumor necrosis factor-alpha, MIP-1-alpha, and LIF levels. Int. J. Radiat. Oncol. Biol. Phys. 15, 1385–1388.
Lupien, S.J., Fiocco, A., Wan, N., Maheu, F., Lord, C., Schramek, T., Tu, M.T., 2005. Stress hormones and human memory function across the lifespan. Psychoneuroendocrinology 30, 225–242.
Lynch, M.A., 2010. Age-related neuroinflammatory changes negatively impact on neuronal function. Front Aging Neurosci. 1, 6.
Marsland, A.L., Gianaros, P.J., Abramowitch, S.M., Manuck, S.B., Hariri, A.R., 2008. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. Biol. Psychiatry. 64, 484–490.
McAfoose, J., Baune, B.T., 2009. Evidence for a cytokine model of cognitive function. Neurosci. Biobeh. Rev. 33, 355–366.
McDonald, B.C., Conroy, S.K., Ahles, T.A., West, J.D., Saykin, A.J., 2010. Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. Breast Cancer Res. Treat. 123, 819–828.
Palmer, S.C., Taggi, A., Demichele, A., Coyne, J.C., 2011. Is screening effective in detecting untreated psychiatric disorders among newly diagnosed breast cancer patients? Cancer 118, 2735–2743.
Phillips, D.C., Woollard, K.J., Griffiths, H.R., 2003. The anti-inflammatory actions of methotrexate are critically dependent upon the production of reactive oxygen species. Br. J. Pharmacol. 138, 501–511.
Phillips, K.M., Jim, H.S., Small, B.J., Laronga, C., Andrykowski, M.A., Jacobsen, P.B., 2012. Cognitive functioning after cancer treatment: a 3-year longitudinal comparison of breast cancer survivors treated with chemotherapy or radiation and noncancer controls. Cancer 118, 1925–1932.
Pickering, M., Oconnor, J., 2007. Pro-inflammatory cytokines and their effects in the dentate gyrus. Prog. Brain Res. 163, 339–354.
Quesnel, C., Savard, J., Ivers, H., 2009. Cognitive impairments associated with breast cancer treatments: results from a longitudinal study. Breast Cancer Res. Treat. 116, 113–123.
Reiss, A.L., Eckert, M.A., Rose, F.E., Karchemskiy, A., Kesler, S., Chang, M., Reynolds, M.F., Kwon, H., Galaburda, A., 2004. An experiment of nature: brain anatomy parallels cognition and behavior in Williams syndrome. J. Neurosci. 24, 5009–5015.
Sabuncu, M.R., Desikan, R.S., Sepulcre, J., Yeo, B.T., Liu, H., Schmansky, N.J., Reuter, M., Weiner, M.W., Buckner, R.L., Sperling, R.A., Fischl, B., 2011. The dynamics of cortical and hippocampal atrophy in Alzheimer disease. Arch. Neurol. 68, 1040–1048.
Schilder, C.M., Seynaeve, C., Beex, L.V., Boogerd, W., Linn, S.C., Gundy, C.M., Huizenga, H.M., Nortier, J.W., van de Velde, C.J., van Dam, F.S., Schagen, S.B., 2010. Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: results from the neuropsychological side study of the tamoxifen and exemestane adjuvant multinational trial. J. Clin. Oncol. 28, 1294–1300.
Seguin, J.A., Brennan, J., Mangano, E., Hayley, S., 2009. Proinflammatory cytokines differentially influence adult hippocampal cell proliferation depending upon the route and chronicity of administration. Neuropsychiatr. Dis. Treat. 5, 5–14.
Seigers, R., Fardell, J.E., 2011. Neurobiological basis of chemotherapy-induced cognitive impairment: a review of rodent research. Neurosci. Biobehav. Rev. 35, 729–741.
Seigers, R., Schagen, S.B., Beerling, W., Boogerd, W., van Tellingen, O., van Dam, F.S., Koolhaas, J.M., Buwalda, B., 2008. Long-lasting suppression of hippocampal cell proliferation and impaired cognitive performance by methotrexate in the rat. Behav. Brain Res. 186, 168–175.
Seigers, R., Schagen, S.B., Coppens, C.M., van der Most, P.J., van Dam, F.S., Koolhaas, J.M., Buwalda, B., 2009. Methotrexate decreases hippocampal cell proliferation and induces memory deficits in rats. Behav. Brain Res. 201, 279–284.
Sephton, S.E., Dhabhar, F.S., Keuroghlian, A.S., Giese-Davis, J., McEwen, B.S., Ionan, A.C., Spiegel, D., 2009. Depression, cortisol, and suppressed cell-mediated immunity in metastatic breast cancer. Brain Behav. Immun. 23, 1148–1155.
Seruga, B., Zhang, H., Bernstein, L.J., Tannock, I.F., 2008. Cytokines and their relationship to the symptoms and outcome of cancer. Nat. Rev. Cancer 8, 887–899.
Spiegel, D., Giese-Davis, J., Taylor, C.B., Kraemer, H., 2006. Stress sensitivity in metastatic breast cancer: Analysis of hypothalamic-pituitary-adrenal axis function. Psychoneuroendocrinology 31, 1231–1244.
Squire, L.R., van der Horst, A.S., McDuff, S.G., Frascino, J.C., Hopkins, R.O., Mauldin, K.N., 2010. Role of the hippocampus in remembering the past and imagining the future. Proc. Natl. Acad. Sci. USA 107, 19044–19048.
Squire, L.R., Wixted, J.T., 2011. The cognitive neuroscience of human memory since H.M. Ann. Rev. Neurosci. 34, 259–288.
Ta, A.T., Huang, S.E., Chiu, M.J., Hua, M.S., Tseng, W.Y., Chen, S.H., Qiu, A., in press. Age-related vulnerabilities along the hippocampal longitudinal axis. Hum. Brain Mapp. http://dx.doi.org/10.1002/hbm.21364.
Tangpong, J., Cole, M.P., Sultana, R., Estus, S., Vore, M., St Clair, W., Ratanachaiyavong, S., St Clair, D.K., Butterfield, D.A., 2007. Adriamycin-mediated nitration of manganese superoxide dismutase in the central nervous system: insight into the mechanism of chemobrain. J. Neurochem. 100, 191–201.
Tangpong, J., Cole, M.P., Sultana, R., Joshi, G., Estus, S., Vore, M., St Clair, W., Ratanachaiyavong, S., St Clair, D.K., Butterfield, D.A., 2006. Adriamycin-induced, TNF-alpha-mediated central nervous system toxicity. Neurobiol. Dis. 23, 127–139.
Tchen, N., Juffs, H.G., Downie, F.P., Yi, Q.L., Hu, H., Chemerynsky, I., Clemons, M., Crump, M., Goss, P.E., Warr, D., Tweedale, M.E., Tannock, I.F., 2003. Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. J. Clin. Oncol. 21, 4175–4183.
Troyer, A.K., Rich, J.B., 2002. Psychometric properties of a new metamemory questionnaire for older adults. J. Gerontol. Ser. B: Psychol. Sci. Soc. Sci. 57, P19–P27.
Tsukiura, T., Sekiguchi, A., Yomogida, Y., Nakagawa, S., Shigemune, Y., Kambara, T., Akitsuki, Y., Taki, Y., Kawashima, R., 2011. Effects of aging on hippocampal and anterior temporal activations during successful retrieval of memory for face-name associations. J. Cogn. Neurosci. 23, 200–213.
Vardy, J., 2009. Cognitive function in breast cancer survivors. Cancer Treat. Res. 151, 387–419.
Vardy, J.L., Booth, C., Pond, G.R., Zhang, H., Galica, J., Dhillon, H., Clarke, S.J., Tannock, I.F., 2007. Cytokine levels in patients (pts) with colorectal cancer and breast cancer and their relationship to fatigue and cognitive function. J. Clin. Oncol. (Meeting Abstracts). 25, 9070-.
Viviani, B., Boraso, M., 2011. Cytokines and neuronal channels: a molecular basis for age-related decline of neuronal function? Exp. Gerontol. 46, 199–206.
Wechsler, D., 2008. Wechsler Adult Intelligence Scale Fourth Edition. TX, The Psychological Corporation, San Antonio.
Wefel, J.S., Vardy, J., Ahles, T., Schagen, S.B., 2011. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 12, 703–708.
Wefel, J.S., Witgert, M.E., Meyers, C.A., 2008. Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. Neuropsychol. Rev. 18, 121–131.
Wilson, C.J., Finch, C.E., Cohen, H.J., 2002. Cytokines and cognition–the case for a head-to-toe inflammatory paradigm. J. Am. Geriatr. Soc. 50, 2041–2056.
Wimmer, M.E., Hernandez, P.J., Blackwell, J., Abel, T., in press. Aging impairs hippocampus-dependent long-term memory for object location in mice. Neurobiol. Aging. http://dx.doi.org/10.1016/j.neurobiolaging.2011.07.007.
Winocur, G., Vardy, J., Binns, M.A., Kerr, L., Tannock, I., 2006. The effects of the anti-cancer drugs, methotrexate and 5-fluorouracil, on cognitive function in mice. Pharmacol. Biochem. Behav. 85, 66–75.
Wolk, D.A., Dickerson, B.C., 2011. Fractionating verbal episodic memory in Alzheimer's disease. Neuroimage 54, 1530–1539.
Wong, M.L., Bongiorno, P.B., al-Shekhlee, A., Esposito, A., Khatri, P., Licinio, J., 1996. IL-1 beta, IL-1 receptor type I and iNOS gene expression in rat brain vasculature and perivascular areas. Neuroreport 7, 2445–2448.
Yirmiya, R., Goshen, I., 2011. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav. Immun. 25, 181–213.
You, Z., Luo, C., Zhang, W., Chen, Y., He, J., Zhao, Q., Zuo, R., Wu, Y., 2011. Pro- and anti-inflammatory cytokines expression in rat's brain and spleen exposed to chronic mild stress: Involvement in depression. Behav. Brain Res. 225, 135–141.